HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ELOCTATE™ safely and effectively. See full prescribing information for ELOCTATE.

ELOCTATE™ [Antihemophilic Factor (Recombinant), Fc Fusion Protein]
Lyophilized Powder for Solution For Intravenous Injection.
Initial U.S. Approval: [2014]

INDICATIONS AND USAGE

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:

- Control and prevention of bleeding episodes
- Perioperative management
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ELOCTATE is not indicated for the treatment of von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

One unit per kilogram body weight will raise the Factor VIII level by 2% international units per deciliter [IU/dL]. Each vial of ELOCTATE is labeled with the amount of recombinant factor VIII in IU. (2)

Dosing formula for bleeding episodes and perioperative management:

Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

OR

Required Dose (IU) = Body Weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

Dosing for routine prophylaxis is: 50 IU/kg every 4 days; it may be adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. More frequent or higher doses up to 80 IU/kg may be required in children less than 6 years of age. (2)

DOSAGE FORMS AND STRENGTHS

ELOCTATE is available as a lyophilized powder in single use vials containing nominally 250, 500, 750, 1000, 1500, 2000, or 3000 international units (IU) of Factor VIII potency. Each vial of ELOCTATE is labeled with the actual content in IU. (3)

CONTRAINDICATIONS

Do not use in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to ELOCTATE.

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, are possible. (5.1)
- Development of Factor VIII neutralizing antibodies (inhibitors) may occur. If expected plasma Factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures Factor VIII inhibitor concentration. (5.2, 5.3)

ADVERSE REACTIONS

Common adverse reactions (incidence ≥1%) observed in clinical trials were arthralgia and malaise. (6)

To report SUSPECTED ADVERSE REACTIONS, contact BIOGEN IDEC at 1-855-693-5628 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clearly needed. (8.1)
- Pediatric: Clearance (based on per kg body weight) is higher in pediatric patients 2 to 5 years of age. Higher or more frequent dosing may be needed. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a recombinant DNA derived, antihemophilic factor indicated in adults and children with Hemophilia A (congenital Factor VIII deficiency) for:

- Control and prevention of bleeding episodes,
- Perioperative management (surgical prophylaxis),
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.

ELOCTATE is not indicated for the treatment of von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

2.1 Dosing Guidelines

- Dose and duration of treatment depend on the severity of the Factor VIII deficiency, the location and extent of bleeding, and the patient's clinical condition. Careful monitoring of replacement therapy is necessary in cases of major surgery or life-threatening bleeding episodes.

- Each vial label of ELOCTATE states the Factor VIII potency in international units (IU). One IU corresponds to the activity of Factor VIII contained in one milliliter of normal human plasma.

- Potency assignment is determined using a chromogenic substrate assay. A field study[1] has indicated that plasma Factor VIII levels can be monitored using either a chromogenic substrate assay or a one stage clotting assay routinely used in US clinical laboratories.

- Calculation of the required dose of Factor VIII is based on the empirical finding that 1 IU of Factor VIII per kg body weight raises the plasma Factor VIII level by 2 IU/dL. The expected *in vivo* peak increase in Factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

  Estimated Increment of Factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

  The dose to achieve a desired *in vivo* peak increase in Factor VIII level may be calculated using the following formula:

Dose (IU) = body weight (kg) x Desired Factor VIII Rise (IU/dL or % of normal) x 0.5 (IU/kg per IU/dL)

- Patients may vary in their pharmacokinetic (e.g., half-life, *in vivo* recovery) and clinical responses. Base the dose and frequency of ELOCTATE on the individual clinical response.
- Dose adjustment may be necessary in pediatric patients under six years of age [*see Use in Specific Populations* (8.4)]. For patients six years of age or older, dose adjustment is not usually required.

Control and Prevention of Bleeding Episodes

A guide for dosing ELOCTATE for the control and prevention of bleeding episodes is provided in Table 1. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 1: Dosing for Control and Prevention of Bleeding Episodes

Type of Bleeding	Factor VIII Level Required (IU/dL or % of normal)	Dose (IU/kg)	Frequency of Dosing (hours)	Duration of Therapy (days)
Minor and Moderate Joint, superficial muscle/no neurovascular compromise (except iliopsoas), deep laceration and renal, superficial soft tissue, mucous membranes	40-60	20-30	Repeat every 24-48 hours (12 to 24 hours for patients less than 6 years of age)	Until the bleeding episode is resolved
Major Life or limb threatening hemorrhage, iliopsoas and deep muscle with neurovascular injury, retroperitoneum, intracranial, or gastrointestinal	80-100	40-50	Repeat every 12-24 hours (8 to 24 hours for patients less than 6 years of age)	Until bleeding is resolved (approximately 7-10 days)

Perioperative Management

A guide for dosing ELOCTATE during surgery (perioperative management) is provided in Table 2. Consideration should be given to maintaining a Factor VIII activity at or above the target range.

Table 2: Dosing for Perioperative Management

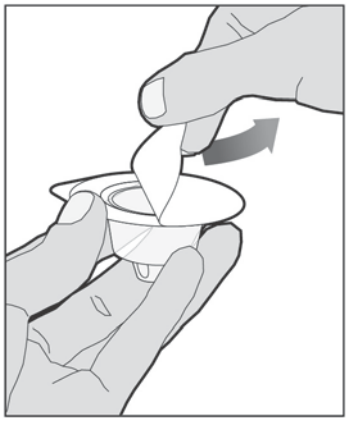
Type of Surgery	Factor VIII Level Required (IU/dL or % of normal)	Dose (IU/kg)	Frequency of Dosing (hours)	Duration of Therapy (days)
Minor Uncomplicated tooth extraction	50-80	25-40	Repeat every 24 hours (12-24 hours for patients less than 6 years of age)	At least 1 day until healing is achieved
Major Intracranial, intra-abdominal, or joint replacement surgery	80-120 (pre- and post-operative)	Preoperative: 40-60 Repeat: 40-50	Pre-operative dose of 40 to 60 IU/kg followed by a repeat dose of 40-50 IU/kg after 8-24 hours (6 to 24 for patients less than 6 years of age) and then every 24 hours to maintain FVIII activity within the target range	Until adequate wound healing, then continue therapy for at least 7 days to maintain a Factor VIII activity within the target range

Routine Prophylaxis

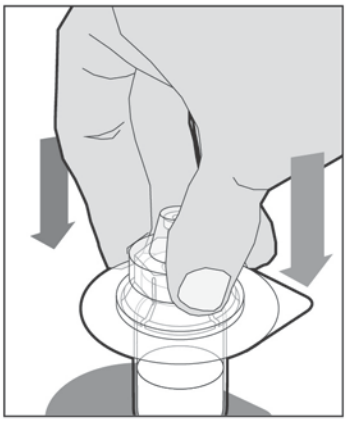
- The recommended starting regimen is 50 IU/kg of ELOCTATE administered every 4 days.
- The regimen may be adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals. More frequent or higher doses up to 80 IU/kg may be required in children less than 6 years of age. [*see Clinical Pharmacology* (12.3)]

2.2 Preparation and Reconstitution

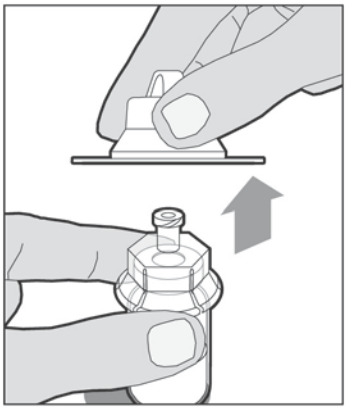
1. Use aseptic technique (clean and germ free) and a flat work surface during the reconstitution procedure.
2. Allow the vial of ELOCTATE and pre-filled diluent syringe to reach room temperature before use.
3. Remove the plastic cap from the vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry.
4. Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the package of the adapter.



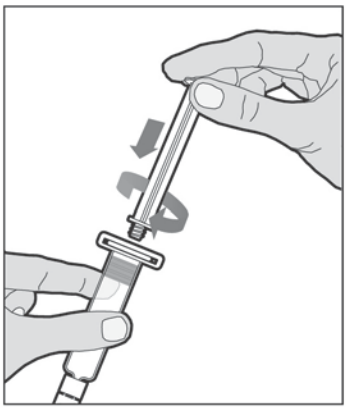
5. Place the vial on a flat and solid surface and use one hand to hold the vial steady. Use the other hand to place the vial adapter over the vial. Place the adapter spike directly above the center of the rubber stopper and push the adapter straight down until the spike punctures the center of the vial stopper and is fully inserted.



6. Lift the package cover away from the vial adapter and discard the cover.



7. Hold the plunger rod at the circular disk. Place the tip of the plunger rod into the end of the syringe. Turn clockwise until it is securely attached. Only use the diluent syringe provided in the ELOCTATE package.



8. With one hand, hold the diluent syringe by the ridged part directly under the cap, with the cap pointing up. Do not use if the cap has been removed or is not securely attached.
9. With your other hand, grasp the cap and bend it at a 90° angle until it snaps off. After the cap snaps off, you will see the glass tip of the syringe. Do not touch the glass tip of the syringe or the inside of the cap.
10. With the vial sitting on a flat surface, insert the tip of the syringe into the adapter opening. Turn the syringe clockwise until it is securely attached to the adapter.
11. Slowly depress the plunger rod to inject all of the diluent into the vial. The plunger rod may rise slightly after this process. This is normal.
12. With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. Do not shake. The reconstituted solution should be clear to slightly opalescent and colorless. Do not use the reconstituted ELOCTATE if it contains visible particles or is cloudy.
13. Make sure the plunger rod is completely depressed. Turn the vial upside-down. Slowly pull on the plunger rod to draw the solution into the syringe. Be careful not to pull the plunger rod completely out of the syringe.
14. Gently unscrew the syringe from the vial adapter and dispose of the vial with the adapter still attached. Do not touch the syringe tip or the inside of the cap.
15. Use the reconstituted ELOCTATE as soon as possible, but no later than 3 hours after reconstitution. Do not touch the glass tip of the syringe if not used immediately after reconstitution. Protect from direct sunlight. **Do not refrigerate after reconstitution.**

To combine two or more vials of ELOCTATE, after step 12 above, follow these pooling steps:

1. Remove the diluent syringe from the vial adapter by turning it counterclockwise until it is completely detached.
2. Leave the vial adapter attached to the vial, as it is needed for attaching a large luer lock syringe (not included in kit). Do not detach the diluent syringe until ready to attach the large luer-lock syringe.

3. Attach a separate, large luer-lock syringe by turning clockwise until it is securely in place.
4. Slowly pull on the plunger rod to draw the solution into the syringe.
5. Repeat this pooling procedure with each vial that is needed to obtain the required dose. When pooling, do not detach the large luer-lock syringe until ready to attach it to the next vial (with vial adapter attached). Once you have pooled the required dose, proceed to administration using the large luer-lock syringe.

2.3 Administration

For intravenous injection only

- Inspect the reconstituted ELOCTATE solution visually for particulate matter and discoloration prior to administration. Do not use if particulate matter or discoloration is observed.
- Do not administer reconstituted ELOCTATE in the same tubing or container with other medications.

Administration Steps:

1. Attach the syringe to the connector end of the infusion set tubing by turning clockwise until it is securely in place.
2. Depress the plunger until all air is removed from the syringe and ELOCTATE has reached the end of the infusion set tubing. Do not push ELOCTATE solution through the needle.
3. Remove the protective needle cover from the infusion set tubing.
4. Perform intravenous bolus infusion. The rate of administration should be determined by the patient's comfort level, and no faster than 10 ml per minute. After infusing ELOCTATE, remove and properly discard the infusion set.

3 DOSAGE FORMS AND STRENGTHS

ELOCTATE is available as a lyophilized powder in single use vials containing nominally 250, 500, 750, 1000, 1500, 2000, or 3000 international units (IU) per vial. The actual Factor VIII potency is labeled on each ELOCTATE vial.

4 CONTRAINDICATIONS

ELOCTATE is contraindicated in patients who have had life-threatening hypersensitivity reactions to ELOCTATE, including anaphylaxis.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, are possible with ELOCTATE. Early signs of hypersensitivity reactions that can progress to anaphylaxis may include angioedema, chest tightness, dyspnea, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to Factor VIII can occur following administration of ELOCTATE. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the plasma Factor VIII level fails to increase as expected or if bleeding is not controlled after ELOCTATE administration, suspect the presence of an inhibitor (neutralizing antibody). [*see Monitoring Laboratory Tests* (5.3)]

5.3 Monitoring Laboratory Tests

- Monitor plasma Factor VIII activity by performing a validated test (e.g., one stage clotting assay), to confirm that adequate Factor VIII levels have been achieved and maintained. [*see Dosage and Administration* (2)]
- Monitor for the development of Factor VIII inhibitors. Perform a Bethesda inhibitor assay if expected Factor VIII plasma levels are not attained, or if bleeding is not controlled with the expected dose of ELOCTATE. Use Bethesda Units (BU) to report inhibitor levels.

6 ADVERSE REACTIONS

Common adverse reactions (≥1% of subjects) reported in clinical trials were arthralgia and malaise.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of one drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice.

In the multi-center, prospective, open-label, clinical trial of ELOCTATE, 164 adolescent and adult, previously treated patients (PTPs, exposed to a Factor VIII containing product for ≥150 exposure days) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) received at least one dose of ELOCTATE as part of either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. A total of 146 (89%) subjects were treated for at least 26 weeks and 23 (14%) subjects were treated for at least 39 weeks.

Adverse reactions (ARs) (summarized in Table 3) were reported for nine (5.5 %) subjects treated with routine prophylaxis or episodic (on-demand) therapy.

Two subjects were withdrawn from study due to adverse reactions of rash and arthralgia. In the study, no inhibitors were detected and no events of anaphylaxis were reported.

Table 3: Adverse Reactions Reported for ELOCTATE (N=164)

MedDRA System Organ Class	MedDRA Preferred Term	Number of Subjects n (%)
General disorders and administration site conditions	Malaise	2 (1.2)
	Chest pain	1 (0.6)
	Feeling cold	1 (0.6)
	Feeling hot	1 (0.6)
Nervous system disorders	Dizziness	1 (0.6)
	Dysgeusia	1 (0.6)
	Headache	1 (0.6)
Musculoskeletal disorders	Arthralgia	2 (1.2)
	Joint swelling	1 (0.6)
	Myalgia	1 (0.6)
Gastrointestinal disorders	Abdominal pain, lower	1 (0.6)
	Abdominal pain, upper	1 (0.6)
Vascular disorders	Angiopathy*	1 (0.6)
	Hypertension	1 (0.6)
Cardiac disorders	Bradycardia	1 (0.6)
Injury, poisoning, and procedural complications	Procedural hypotension	1 (0.6)
Respiratory, thoracic, and mediastinal disorders	Cough	1 (0.6)

Skin and subcutaneous tissue disorders	Rash	1 (0.6)

*Investigator term: vascular pain after injection of study drug

6.2 Immunogenicity

Clinical trial subjects were monitored for neutralizing antibodies to Factor VIII. No subjects developed confirmed, neutralizing antibodies to Factor VIII. One 25 year old subject had a transient, positive, neutralizing antibody of 0.73 BU at week 14, which was not confirmed upon repeat testing 18 days later and thereafter.

The detection of antibodies that are reactive to Factor VIII is highly dependent on many factors, including: the sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications and underlying disease.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproductive studies have not been conducted with ELOCTATE. It is not known whether or not ELOCTATE can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. ELOCTATE should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

It is not known whether or not ELOCTATE is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when ELOCTATE is administered to a nursing woman.

8.4 Pediatric Use

Pharmacokinetic studies in children have demonstrated a shorter half-life and lower recovery of Factor VIII compared to adults. Because clearance (based on per kg body weight) has been shown to be significantly higher in the younger, pediatric population (2 to 5 years of age), higher and/or more frequent dosing based on body weight may be needed. [*see Clinical Pharmacology* (12.3)]

Safety and efficacy studies have been performed in 56 previously treated, pediatric patients <18 years of age who received at least one dose of ELOCTATE as part of routine prophylaxis, on-demand treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent safety and efficacy trial, and subjects <12 were enrolled in an ongoing pediatric trial. Twelve subjects (21%) were <6 years of age, 31 (55%) subjects were 6 to <12 years of age, and 13 subjects (23%) were adolescents (12 to <18 years of age). Interim pharmacokinetic data from a pediatric study of the 38 subjects <12 years of age showed that no dose adjustment had been required for patients ≥6 years old. Children age 2 to 5 years had a shorter half-life and

higher clearance (adjusted for body weight); therefore, a higher dose or more frequent dosing may be needed in this age group. [*see Clinical Pharmacology* (12.3)]

8.5 Geriatric Use

Clinical studies of ELOCTATE did not include sufficient numbers of subjects aged 65 and over to determine whether or not they respond differently from younger subjects.

11 DESCRIPTION

ELOCTATE, Antihemophilic Factor (Recombinant), Fc Fusion Protein, is a sterile, non-pyrogenic, lyophilized powder for reconstitution for intravenous injection. The product is supplied in single use vials containing nominal potencies of 250, 500, 750, 1000, 1500, 2000 or 3000 international units (IU). Each vial of ELOCTATE is labeled with the actual content in IU. The powder for injection is reconstituted with 3 mL sterile water for injection (SWFI) supplied in a sterile prefilled syringe. The reconstituted product contains the excipients: sucrose, sodium chloride, L-histidine, calcium chloride and polysorbate 20. ELOCTATE contains no preservatives.

B-domain deleted recombinant Factor VIII, Fc fusion protein (BDD-rFVIIIFc) is the active ingredient in ELOCTATE. BDD-rFVIIIFc is a recombinant protein consisting of a B-domain deleted analogue of human Coagulation Factor VIII covalently linked to the human immunoglobulin G_1 (IgG_1) Fc domain sequence. The Factor VIII portion of the molecule has a 90 kDa heavy chain and an 80 kDa light chain (similar to endogenous Factor VIII), which are linked by 14 (of 908) amino acids from the central B-domain. The FVIII portion has post-translational modifications comparable to endogenous Factor VIII. The Fc domain of the molecule contains the hinge, CH2, and CH3 regions of IgG_1. BDD-rFVIIIFc contains 1890 amino acids with an apparent molecular weight of 220 kDa. The majority of the expressed protein is proteolytically processed to a two chain molecule; however ELOCTATE may also contain up to 39% of a single chain, non-processed form. Both molecules have been shown to have comparable Factor VIII activity.

BDD-rFVIIIFc is produced by recombinant DNA technology from a human embryonic kidney (HEK) cell line, which has been extensively characterized. The HEK cell line expresses BDD-rFVIIIFc into a defined, cell culture medium that does not contain any proteins derived from animal or human sources. BDD-rFVIIIFc is purified using a series of chromatography steps, including affinity capture with a recombinant, single chain antibody fragment produced in a yeast expression system. No human or animal derived proteins are used in the purification or formulation processes. The production process also incorporates two dedicated viral clearance steps - a detergent treatment step for inactivation and a 15 nm filtration step for removal of viruses.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ELOCTATE is a recombinant fusion protein that temporarily replaces the missing Coagulation Factor VIII needed for effective hemostasis. ELOCTATE contains the Fc

region of human immunoglobulin G_1 (IgG_1), which binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation and prolonging their plasma half-life.

12.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation Factor VIII, resulting in a prolonged, patient plasma clotting time as measured by the activated partial thromboplastin time (aPTT) assay. Treatment with ELOCTATE™ normalizes the aPTT over the effective dosing period.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of ELOCTATE™ (rFVIIIFc) were evaluated in 28 subjects following a 10 minute intravenous infusion of a single dose of 50 IU/kg. The PK parameters (Table 4) were based on plasma FVIII activity measured by the one-stage clotting assay. The PK profile obtained at week 14, after repeated dosing, was comparable with the PK profile obtained after the first dose. The PK data demonstrate that ELOCTATE™ has a prolonged circulating half-life.

Table 4: Pharmacokinetic Parameters (Arithmetic Mean, 95% CI)

PK Parameters	rFVIIIFc (95% CI) N=28
C_{max} (IU/dL)	**109** (102, 116)
AUC/Dose (IU x h/dL per IU/kg)	**54.1** (47.0, 61.1)
Terminal half-life (h)	**19.7** (17.4, 22.0)
CL (mL/h/kg)	**2.06** (1.78, 2.34)
MRT (h)	**26.1** (23.2, 28.9)
V_{ss} (mL/kg)	**49.5** (46.9, 52.2)
Incremental Recovery (IU/dL per IU/kg)	**2.26** (2.13, 2.40)
Time to 1% (days)	**5.10** (4.54, 5.66)

Abbreviations: CI = confidence interval; Cmax = maximum observed activity; AUC= area under the curve; MRT = mean residence time; CL = clearance; Vss = body weight adjusted volume of distribution at steady-state; Time to 1% = time after dose when FVIII activity has declined to 1 IU/dL above baseline.

Pediatric and Adolescent Pharmacokinetics

Pharmacokinetic (PK) parameters of ELOCTATE were determined for adolescents (ages 12 to 17 years) in the phase 3 study and for children (ages 2 to 5 years and 6 to 11 years) in an open-label, multi-center study of pediatric, previously treated patients. [*see Pediatric Use* (8.4)]

Table 5 presents the PK parameters calculated from the pediatric data of 48 subjects, less than 18 years of age, after receiving a single 50 IU/kg dose. Compared to adults and adolescents, body weight adjusted clearance was higher in children 2 to 5 years of age. These results indicate a need for dose adjustments in children 2 to 5 years of age. [*see Pediatric Use* (8.4)]

The PK evaluation of pediatric subjects, ages 6 to 17 years, showed that their PK profiles and arithmetic means of PK parameters are similar to those of adults. Therefore, for subjects 6 years and older, an age-based dose adjustment is not required.

Table 5: Comparison of PK Parameters of ELOCTATE by Age

PK Parameters[1]	**Pediatric Study**		**Phase 3 Study**
	2 to 5 Years	**6 to 11 Years**	**12 to 17 Years**
	N = 10	**N = 27**	**N = 11**
IR (IU/dL per IU/kg)	1.89 (1.75, 2.03)	2.44 (2.02, 2.85)	1.85 (1.58, 2.12)
AUC/Dose (IU*h/dL per IU/kg)	28.3 (22.1, 34.5)	43.7 (35.1, 52.3)	38.7 (34.3, 43.1)
$t_{½}$ (h)	12.0 (9.55, 14.4)	14.6 (11.5, 17.7)	16.4 (14.1, 18.6)
MRT (h)	16.4 (13.0, 19.7)	21.1 (16.8, 25.5)	23.1 (19.9, 26.4)
CL (mL/h/kg)	3.88 (2.91, 4.49)	2.70 (2.30, 3.09)	2.66 (2.34, 2.98)
V_{ss} (mL/kg)	58.7 (54.7, 62.6)	49.9 (44.5, 55.3)	60.3 (53.3, 67.3)

[1]PK parameters are presented in Arithmetic Mean (95% CI)

Abbreviations: CI = confidence interval; IR=incremental recovery; AUC = area under the FVIII activity time curve; $t_{1/2}$ = elimination half-life; MRT = mean residence time; CL = body weight adjusted clearance; Vss = body weight adjusted volume of distribution at steady-state

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long term animal studies investigating the carcinogenic effects of ELOCTATE have not been conducted. *In vitro* and *in vivo* testing of ELOCTATE for mutagenicity or effects on fertility was not performed.

14 CLINICAL STUDIES

The safety and efficacy of ELOCTATE was evaluated in a multi-center, prospective, open-label, clinical trial that compared the efficacy of each of two prophylactic treatment regimens (individualized interval and fixed weekly) to episodic (on-demand) treatment; determined hemostatic efficacy in the treatment of bleeding episodes; and determined hemostatic efficacy during perioperative management in subjects undergoing major surgical procedures. The study enrolled a total of 165 previously treated male patients (PTPs) with severe Hemophilia A (<1% endogenous Factor VIII activity or a genetic mutation consistent with severe Hemophilia A). Subjects were aged 12 to 65 years, including 13 pediatric subjects aged 12 to 17 years. Of the 165 enrolled subjects, 164 received at least one dose of ELOCTATE and 163 (98%) were evaluable for efficacy. A total of 153 subjects (93%) completed the study.

Control and Prevention of Bleeding Episodes

A total of 757 bleeding episodes in 106 subjects were treated with ELOCTATE. The majority of the bleeding episodes were spontaneous and localized in joints. The median dose per injection used to treat a bleeding episode was 27.35 (IQR 22.73, 32.71) IU/kg. Assessment of response to each injection was recorded by subjects at 8-12 hours after treatment. Efficacy in control of bleeding episodes is summarized in Table 6.

Table 6: Summary of ELOCTATE Efficacy in Control of Bleeding

New bleeding episodes		(n = 757)
# of Injections to treat bleeding episodes		
	1 injection	661 (87.3%)
	2 injections	79 (10.4%)
	3 injections	13 (1.7%)
	≥4 injections	4 (0.5%)
Response to first injection*		(n = 745)
	Excellent or good	78.1%
	Moderate	21.2%
	No response	0.7%

*Excellent: abrupt pain relief and/or improvement in bleeding; Good: definite pain relief and/or improvement in signs of bleeding but possibly requiring more than one injection; Moderate: probable beneficial effect and requiring more than one injection; No response: no improvement or condition worsens. Response evaluated at approximately 8-12 hours after treatment.

Perioperative Management

Nine major surgical procedures (two laparoscopic, inguinal hernia repairs, five knee surgeries, one appendectomy and one arthroscopy) were performed in nine subjects. The median, pre-operative dose was 51 IU/kg (range 50 – 77). The total dose on the day of surgery ranged from 66 to 115 IU/kg. The hemostatic response for all but one surgery was rated as excellent (blood loss/transfusions less than or similar to a nonhemophilic patient; no extra dose of ELOCTATE needed) and the remaining surgery was rated as good (blood loss no more than 250 mL greater than expected, no extra dose of ELOCTATE needed). An additional 14 minor surgical procedures were performed in 12 subjects. Hemostatic response was available for 12 minor surgeries; it was rated as excellent for 11 and good for 1.

Routine Prophylaxis

The efficacy of routine prophylaxis (individualized and fixed-weekly regimens) was evaluated against on-demand treatment. A total of 117 subjects received an individualized, twice weekly regimen, which started with 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. The dose and interval were adjusted within the range of 25 – 65 IU/kg every 3-5 days to maintain trough levels between 1% and 3% above baseline, or higher, as clinically indicated to prevent bleeding. The median dosing interval was 3.5 days. Among the 112 subjects treated for at least 6 months, 111 (99%) achieved a dosing interval of three days or longer, 39 (35%) achieved a dosing interval of 4 days or longer, and 33 (29%) achieved a dosing interval of 5 days or longer during the last 3 months on study. Twenty-three subjects received 65 IU/kg of ELOCTATE once weekly for a median period of 28 weeks. An additional 23 subjects received episodic (on-demand) doses of ELOCTATE for the treatment of bleeding episodes and were on study for a median period of 29 weeks. Using a negative binomial model to analyze the annualized bleeding rate (ABR), there was a statistically significant reduction in ABR of 92% ($p<0.001$) for subjects in the individualized prophylaxis arm and a statistically significant reduction of 76% ($p<0.001$) for subjects in the weekly prophylaxis arm compared to the episodic (on-demand) arm. Fifty-three (53) of 117 (45%) subjects experienced no bleeding episodes while on individualized prophylaxis and 4 of 23 (17%) subjects experienced no bleeding episodes while on weekly prophylaxis.

Median ABRs in subjects evaluable for efficacy is summarized in Table 7.

Table 7: Median (IQR)[1] Annualized Bleed Rate by ELOCTATE Treatment Arm

Bleeding Episode Etiology	Individualized Prophylaxis (N=117)	Weekly Prophylaxis (N=23)	Episodic (On-Demand) (N=23)
Overall ABR	1.60 (0.0, 4.69)	3.59 (1.86, 8.36)	33.57 (21.14, 48.69)
Spontaneous ABR	0.00 (0.0, 2.03)	1.93 (0.0, 4.78)	20.24 (12.21, 36.81)
Joint ABR	0.00 (0.00, 3.11)	1.93 (0.00, 7.62)	22.76 (15.07, 39.02)

[1] Median (interquartile range, 25th and 75th percentiles)

15 REFERENCES

1. Sommer JM, Moore N, McGuffie-Valentine B, et al. Comparative field study evaluating the activity of recombinant factor VIII Fc fusion protein in plasma samples at clinical haemostasis laboratories. Haemophilia. 2014;20 : 294 – 300.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ELOCTATE is supplied in kits comprising a single use vial containing nominally, 250, 500, 750, 1000, 1500, 2000, or 3000 international units (IU) of Factor VIII potency, a pre-filled syringe with 3 mL sterile water for injection, and a sterile vial adapter (reconstitution device). The actual amount of ELOCTATE in IU is stated on the label and carton of each vial.

Strength	Kit NDC Number
250 IU	64406-801-01
500 IU	64406-802-01
750 IU	64406-803-01
1000 IU	64406-804-01
1500 IU	64406-805-01
2000 IU	64406-806-01
3000 IU	64406-807-01

Storage and Handling

Prior to reconstitution:

- Store ELOCTATE in the original package to protect the ELOCTATE vials from light.
- Store ELOCTATE in powder form at 2°C to 8°C (36°F to 46°F). Do not freeze to avoid damage to the pre-filled diluent syringe.
- ELOCTATE may be stored at room temperature, not to exceed 30°C (86°F), for a single period of up to 6 months, within the expiration date printed on the label.
- If stored at room temperature, record the date that ELOCTATE is removed from refrigeration on the carton in the area provided. After storage at room temperature, do not return the product to the refrigerator.
- Do not use beyond the expiration date printed on the vial or 6 months after the date that was written on the carton, whichever is earlier.

After Reconstitution:

- The reconstituted product may be stored at room temperature, not to exceed 30°C (86°F), for up to 3 hours. Protect from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded.
- Do not use ELOCTATE if the reconstituted solution is cloudy or has particulate matter.
- Discard any unused ELOCTATE.

17 PATIENT COUNSELING INFORMATION

Advise the patients to:

- Read the FDA approved patient labeling (Patient Information and Instructions for Use)

- Call their healthcare provider or go to the emergency department right away if a hypersensitivity reaction occurs. Early signs of hypersensitivity reactions may include rash, hives, itching, facial swelling, tightness of the chest, and wheezing.
- Report any adverse reactions or problems following ELOCTATE administration to their healthcare provider.
- Contact their healthcare provider or treatment facility for further treatment and/or assessment if they experience a lack of a clinical response to Factor VIII therapy because this may be a sign of inhibitor development.

44279-01

Manufactured by:

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Cambridge, MA 02142 USA
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FDA-Approved Patient Labeling

Patient Information

ELOCTATE™ /el' ok' tate /
[Antihemophilic Factor (Recombinant), Fc Fusion Protein]

Please read this Patient Information carefully before using ELOCTATE and each time you get a refill, as there may be new information. This Patient Information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is ELOCTATE?

ELOCTATE is an injectable medicine that is used to help control and prevent bleeding in people with Hemophilia A (congenital Factor VIII deficiency).

Your healthcare provider may give you ELOCTATE when you have surgery.

Who should not use ELOCTATE?

You should not use ELOCTATE if you had an allergic reaction to it in the past.

What should I tell my healthcare provider before using ELOCTATE?

Talk to your healthcare provider about:

- Any medical problems that you have or had.
- All prescription and non-prescription medicines that you take, including over-the-counter medicines, supplements or herbal medicines.
- Pregnancy or if you are planning to become pregnant. It is not known if ELOCTATE may harm your unborn baby.
- Breastfeeding. It is not known if ELOCTATE passes into the milk and if it can harm your baby.

How should I use ELOCTATE?

You get ELOCTATE as an infusion into your vein. Your healthcare provider will instruct you on how to do infusions on your own, and may watch you give yourself the first dose of ELOCTATE.

Contact your healthcare provider right away if bleeding is not controlled after using ELOCTATE.

What are the possible side effects of ELOCTATE?

Common side effects of ELOCTATE are joint pain and general discomfort.

Allergic reactions may occur. Call your healthcare provider or emergency department right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash or hives.

Your body can also make antibodies called, “inhibitors,” against ELOCTATE, which may stop ELOCTATE from working properly. Your healthcare provider may give you blood tests to check for inhibitors.

How should I store ELOCTATE?

- Keep ELOCTATE in its original package.
- Protect it from light.
- Do not freeze.
- Store refrigerated (2°C to 8°C or 36°F to 46°F) or at room temperature [not to exceed 30°C (86°F)], for up to six months.
- When storing at room temperature:
  - Note on the carton the date on which the product is removed from refrigeration.
  - Use the product before the end of this 6 month period or discard it.
  - Do not return the product to the refrigerator.

Do not use ELOCTATE after the expiration date printed on the vial or, if you removed it from the refrigerator, after the date that was noted on the carton, whichever is earlier.

After reconstitution (mixing with the diluent):

- Do not use ELOCTATE if the reconstituted solution is not clear to slightly opalescent and colorless.
- Use reconstituted product as soon as possible
- You may store reconstituted solution at room temperature, not to exceed 30°C (86°F), for up to three hours. Protect the reconstituted product from direct sunlight. Discard any product not used within three hours.

What else should I know about ELOCTATE?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use ELOCTATE for a condition for which it was not prescribed. Do not share ELOCTATE with other people, even if they have the same symptoms that you have.

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